# THE PROBLEM OF ELEVATED BLOOD CHOLESTEROL

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ATHEROSCLEROSIS is the basic disease process responsible for clinical coronary heart disease. The role of elevated blood cholesterol in the pathogenesis of atherosclerosis is therefore the focal point of this brief presentation. Its basic theses are that serum cholesterol and atherogenesis are interrelated in a very significant way, and that this interrelationship is of great importance for the contemporary practice of clinical medicine and public health.

The evidence supporting this thesis comes from all three basic research methodologies available to modern medicine, i.e., clinical-pathologic research, animal-experimental research, and epidemiologic research.

The origins of our contemporary understanding of this problem go back at least 200 years.* Early necropsy studies in gross pathology yielded the first leads. Thus, Albrecht von Haller in 1755 described aortic atherosclerosis, noting that yellow soft mushy atheromatous material effused between medial and intimal layers. He concluded that a gradual evolution occurred from the soft state of atheroma to a final scarified, calcified, and ossified lesion. The monumental microscopic studies in cellular pathology during the second half of the 19th century, initiated by Virchow and his colleagues, led to the delineation of atherosclerosis as a distinct pathologic entity in the generic group of the arteriosclerоses. This advance stemmed from the recognition and elucidation of the unique morphologic characteristic of the atherosclerotic plaque. It was demonstrated that the mushy, gruel-like material ("athere," Greek for mush)—the hallmark of the lesion—was an accumulation of lipid, including cholesterol. This identification of cholesterol-lipid inevitably posed critical questions: At what state of atherogenesis does deposition of cholesterol-lipid occur? Is this an early, primary event or a late, secondary event? What is the relationship between fat in the diet and lipid in the lesion? All these critical questions had been posed with more or less clarity by the turn of the present century. And several of the early workers, among them Virchow, formulated and adhered to an infiltration theory, i.e., the concept that the atheromatous material is derived by imbibition from the plasma.

In subsequent decades biochemical pathology elaborated these observations and concepts of morphologic pathology. It was demonstrated that atherosclerotic arteries invariably exhibit significant increases in their content of cholesterol and other lipids. Moreover, considerable direct evidence was obtained supporting the infiltration theory, particularly with respect to the derivation of lesion cholesterol from plasma cholesterol.

A second fundamental contribution was made late in the 19th and early in the 20th century by clinical investigation. This research went a step beyond the post-mortem findings of pathology on the problem of the relationship of serum cholesterol to atherogenesis. It was noted that prolonged hypercholesterolemia occurred in a series of diseases, i.e.,

* Many extensive reviews with comprehensive bibliographies on atherosclerosis are available. Therefore, no attempt is made in the present report to present bibliographic documentation. The interested reader is referred to several of these reviews.[1-16]

diabetes mellitus, hypothyroidism, the nephrotic syndrome, essential familial xanthomatosis. Premature severe atherosclerosis was a common finding in patients with these diseases. This generalization closely linked hypercholesterolemia and atherogenesis. It has received firm support from recent studies of these diseases.

A third basic contribution—from the animal experiment laboratory — was made in the period 1908-1912 by Anitschkow and his collaborators. Prior to this time, extensive efforts had been made to reproduce the lesion of human atherosclerosis in laboratory animals—without success. These fruitless attempts, of course, were stimulated by the specific hypotheses of their authors concerning the etiology and pathogenesis of atherosclerosis. Thus, investigators projecting a toxin hypothesis injected animals with toxins; those advancing a mechanical trauma hypothesis traumatized arteries; and so forth. Not unexpectedly, vascular lesions resulted in many of these experiments, but never atherosclerosis.

Anitschkow's breakthrough came in nutritional experiments in rabbits. It was noted that rabbits fed animal tissues developed hyperlipemia and atherosclerosis. Subsequent experiments demonstrated that the atherogenic material in the animal tissues was cholesterol and fat—and not protein.

These studies were vigorously followed up during subsequent decades. In the years since World War II, further major successes have been achieved. By now atherosclerosis has been induced in every experimental animal worked with in the laboratory (omnivorous, carnivorous, herbivorous, avian and mammalian, including primates). Almost without exception, these successes have been achieved by means of a change in diet (with or without other forms of intervention), including an increased intake of cholesterol and fat, leading to a sustained hypercholesterolemic hyperlipemia. This nutritional-metabolic alteration is a virtual sine qua non for experimental atherogenesis.

This generalization from the animal experimental work is of decisive importance for our understanding of the relationship among diet, cholesterolemia, and atherogenesis. Of equal importance is the demonstration that the lesions may regress and even disappear completely in animals, when normal nutrition is restored and hypercholesterolemia reversed.

These findings of experimental atherosclerosis support the concept that elevated serum cholesterol is a key factor in the pathogenesis of atherosclerosis. In addition, they support the concept that habitual dietary patterns may be of great importance in the production of hypercholesterolemia and atherogenesis.

A fourth contribution stems from clinical investigation. It was the demonstration that serum cholesterol levels are elevated in groups of middle-aged men* with clinical coronary heart disease, compared to control groups. Data along these lines began to appear in the early 1920's, and have accumulated in a massive way since World War II. The recent studies show that the younger the two groups, diseased and clinically normal, the greater the differences in serum cholesterol.

It is important to appreciate that these comparisons are not actually between groups of persons with and without atherosclerotic disease; for autopsy studies in Americans clearly demonstrate that coronary atherosclerosis is virtually omnipresent in our adult male population. That is, most of the "normals" among Americans are not truly normal with respect to atherosclerosis, or with respect to cholesterolemia, for that mat-

* A discussion of the sex difference in coronary disease incidence in middle-age, i.e., the relative resistance of woman and susceptibility of men under modern American conditions, is beyond the scope of this report; cf. refs. 3, 6, 8, 12–15.

ter (see below). Most of the "normals" actually belong in the subclinical (or preclinical) submerged portion of the iceberg that is atherosclerotic disease. The comparison therefore is between groups with more and less severe disease. Despite the fact that this is not a "clean" positive-negative comparison, the data are unequivocal. They demonstrate higher cholesterol levels in middle-aged groups with clinical coronary disease, compared with controls. And if the comparison is made between coronary disease groups in the United States and normal groups from many other countries (see below), then the differences are conspicuously greater.

The next major contribution elucidating the relationship between cholesterolemia and atherosclerosis has come from epidemiologic research. Here too, data have been accumulating for a number of decades. The earlier work demonstrated a correlation in populations between habitual dietary patterns and occurrence rates of morphologic atherosclerosis and atherosclerotic disease. In populations habitually subsisting on diets high in animal foodstuffs, including dairy products, the lesion and the disease were invariably common. In contrast, populations with a life-span pattern of diet predominantly vegetarian had low occurrence rates.

This was the correlation indicated by the data available prior to World War II. Since then, the use of the epidemiologic method in atherosclerosis research has been greatly extended. The foregoing correlation has been amply confirmed. Moreover, an additional major correlation has been demonstrated—among habitual diets, plasma cholesterol levels, and atherosclerotic disease occurrence rates. The differences are particularly conspicuous when comparisons are made between middle-aged populations from the United States and from the economically less developed countries of Africa, Asia, and Latin America. Thus, mean serum cholesterol levels of clinically normal middle-aged American men are in the order of 240 mg per cent. In contrast, South African Bantu show mean levels of about 180 mg per cent; Guatemalan handicraft and agricultural workers of about 140 mg per cent; manual laborers in India about 125 mg per cent. The differences in intakes of total calories, total fats, saturated fats, refined carbohydrates and cholesterol, and in occurrence rates of coronary disease in middle-age are correspondingly marked.

Studies on social class differences and on the effects of migration add an additional dimension to these data. Thus, middle and upper class groups in Guatemala and India have mean serum cholesterol levels of about 200 mg per cent, in contrast to the lower levels in manual laborers in these countries. Correspondingly, patterns of diet and disease occurrence in wealthier Guatemalans and Indians tend to approach those of North Americans, rather than those of their poorer fellow countrymen.

Similarly, groups of migrants—Japanese from Japan to Hawaii or the United States, Yemenite Jews from Yemen to Israel, Neapolitans from Naples to Boston, undergo sizable increases in levels of cholesterolemia and in occurrence rates of atherosclerotic disease. These supervene pari passu with changes in mode of living in general and diet in particular. These findings not only lend further weight to the validity—and etiologic implications—of the three-way correlation among diet, serum cholesterol, and atherosclerotic disease. They also strongly indicate that such factors as race, ethnic origin, climate, and geography are of little or no etiologic significance. Thus, the massive epidemiologic data strongly support the concepts that cholesterolemia and atherogenesis in populations are closely related pathogenetically, and that diet is a key etiologic influence on both of these.

Recent epidemiologic studies within the United States have yielded impressive additional evidence on these interrelationships. Thus, differences in serum cholesterol levels in groups of middle-aged American men are associated with marked differences in risk of developing clinical coronary disease. These differences in risk are in the order of 3-6 to 1. The data of the Framingham study, for example, demonstrate an incidence rate of clinical coronary heart disease of 13/1.000/4 years in men aged 45-62 with cholesterol levels under 225 mg per cent. In contrast, the incidence rate was 80/1.000/4 years in the group with cholesterol levels of 260 mg per cent or above. These data, incidentally, serve to illuminate the longstanding problem of proper standards for normal serum cholesterol.

Epidemiologic data of another type add further evidence concerning the relationship between cholesterolemia and atherosclerosis. In our study in a Chicago utility company, middle-aged white males were stratified by such variables as occupation, physical activity of work, white collar vs. blue collar work, indoor vs. outdoor work, sedentary vs. nonsedentary work, education, income. Virtually all groups exhibited similar mean serum cholesterol levels in the order of 240 mg per cent. Prevalence rates for frank hypercholesterolemia — values of 260 mg per cent or greater—were in the order of 300/1,000 for all groups. Prevalence rates of hypertension and obesity were also very similar in all groups, at about the level of 200/1,000. Correspondingly, all socioeconomic groups exhibited high incidence rates of coronary heart disease, in the order of 60/1,000/4 years.

These data lend further weight to the concept that high mean serum cholesterol levels and high prevalence rates of hypercholesterolemia in middle-aged male populations are associated with high occurrence rates of coronary disease.

Data on dietary patterns of different socioeconomic groups in the United States demonstrate a remarkable uniformity, and are correlated with the foregoing findings. Virtually all strata ingest diets high in total calories, total fats, saturated fats, refined carbohydrates, and cholesterol. Recent epidemiologic studies across the country have repeatedly yielded like findings on these matters. Therefore, the three-way correlation — among habitual diet, serum cholesterol and coronary disease—holds for most groups in the American population at midcentury.

Thus far attention in this presentation has been given almost exclusively to the role of hypercholesterolemia, as a single variable, in the pathogenesis of atherosclerotic disease. It has been noted that this one abnormality by itself is associated with a three- to six-fold increase in the risk of clinical coronary disease in middle-aged men. Based on the recent research evidence, it is now possible to go a step further. The previous speaker,* for example, focused on elevated blood pressure as a key variable increasing risk of coronary disease. This is entirely valid. Hypertension too is associated with a three- to six-fold increase in risk. Other abnormalities associated with increased risk of premature coronary disease are: obesity, diabetes mellitus, hypothyroidism, renal damage, heavy smoking, a family history of premature vascular disease, possibly sedentary living, perhaps psychological stress-strain-tension.

The interrelated influences of three of these variables — hypercholesterolemia, hypertension, and obesity—have by now been quantitated fairly precisely. Thus, middle-aged men normal with respect to all three of these had a coronary disease incidence rate of only 10/1,000/4 years, according to the Framingham study;

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the group with two or three abnormalities had a rate of 143/1,000/4 years; a 14-fold difference in risk! Thus the findings of clinical and epidemiologic research have made it quite a simple matter to identify the coronary-prone, high-risk, susceptible persons in our population.

The last major contribution concerning cholesterolemia and atherosclerosis comes from recent clinical research. In the last few years it has been unequivocally shown that hypercholesterolemia can be lowered by nutritional means in most cases. This can be achieved in either of two ways, i.e., by use of diets low in total fats-cholesterol, or by use of oil-containing diets, moderate in total fat content (25-30 per cent of total calories) and low in saturated fats (10 per cent or less of total calories) and cholesterol. Serum cholesterol can usually be reduced by such nutritional regimens without recourse to either pills or jiggers of oil. These diets may also be effectively used for correcting and preventing obesity. Particularly those using oils are palatable, pleasant, and varied. They permit a very delectable cuisine, as well as optimal nutrition. They are readily utilizable and adaptable by ordinary, free-living individuals.

The ability of such diets, made up of mixed ordinary foodstuffs, to achieve reduction of hypercholesterolemia in most free-living subjects has already been well documented in the published reports of Jolliffe, Page, and others, and in the experiences during the last 18 months of our Coronary Prevention Evaluation Program at the Chicago Board of Health. On the average, a 15 to 20 per cent decrease in hypercholesterolemia is readily achieved.

It is worth while, in closing, to speculate concerning the possible significance for public health and preventive medicine of these massive findings on diet, cholesterolemia and atherosclerosis. Consider the following projection: A 15 per cent lowering of the serum cholesterol of middle-aged American men would yield a mean serum cholesterol level of about 204 mg per cent. A 20 per cent reduction would result in a mean level of about 191 mg per cent. The entire distribution curve would shift correspondingly to the left. Instead of a hypercholesterolemia prevalence rate of 300/1,000, it would decline to about 100/1,000 or 45/1,000.

Continuing this speculative projection, the possible effect on incidence rates of premature coronary disease can be estimated hypothetically with quantitative accuracy based on current data. Leaving aside any possible concomitant effects of altered nutritional patterns on other risk factors, e.g., obesity and hypertension, a 15 to 20 per cent reduction in mean serum cholesterol levels alone might be associated with a 25 to 50 per cent reduction in coronary disease incidence rates in middle-aged men.

Coronary heart disease is our major public health problem in the United States today, exacting a terrible toll, not only among the elderly, but as well among the middle-aged. It is truly our Number One epidemic disease at midcentury, as data on incidence and mortality rates clearly demonstrate. As with other epidemic diseases, a principal task of public health and preventive medicine is to identify the susceptibles. This is a first basis for an effective attempt at prophylaxis. Research since World War II has revealed the means for identifying the high risk, coronary prone, susceptible persons before clinical events ensue. They are easy to distinguish, using a series of simple medical determinations—the measurement of weight, blood pressure, serum cholesterol, thyroid function, carbohydrate metabolism: the assessment of kidney status, family history, smoking status, physical activity status.

Except for sex and heredity, all the findings associated with increased risk

of coronary disease are generally amenable to correction and/or control by simple, safe means. Nutrition is a cornerstone of these corrective measures.

The problem remains: How valid is the foregoing speculative projection? How much prevention of coronary disease can be achieved by correction of abnormalities making for susceptibility? Definitive answers to these questions are not yet in, and will probably not be available for five to ten years. However, suggestive information of an encouraging kind is extant.

We are therefore faced with the temporary problem of what to do during this interim period. The elementary data on incidence and mortality rates—considered against the background of the research achievements—seem to compel an unequivocal answer: an incidence rate of 1,000-1,500/100,000/year with from 25 to 30 per cent of first attacks acutely fatal;* a mortality rate of 330/100.000/year in men aged 45-54, with one-third of all deaths in this middle-aged group due to coronary disease. There is no reason to believe that a policy of "watchful waiting"—pending the completion of research studies on prevention during the next decade—will in any way alter this grim picture. On the other hand, the measures proposed for prophylaxis in high risk persons are safe, moderate, sound, and free of danger. And a wealth of evidence points to the likelihood of their value. Their widespread prophylactic utilization by clinical medicine and public health would therefore seem to be the order of the day.

* This fatality rate includes cases dying suddenly and cases not reaching the hospital.

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